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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/631,863	08/03/2000	Renate Konopitzky	12/211	8920

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/631,863	KONOPITZKY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-16,18-32 and 34-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2 and 4* is/are allowed.

6)☒ Claim(s) *3,5 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels clams 17 and 34.

Accordingly, claims 1-5, 33 are examined in the instant application.

Claims 1-2, 4 are free of prior art and seem to be allowable.

The following are the remaining rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 3, 5, 33 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for 1) a fragment of SEQ ID NO:2, wherein said fragment is presented by an MHC-molecule and induces or augments a cellular immune response, or a fragment of SEQ ID NO:2, wherein said fragment induces or augments a humoral immune response and 2) a pharmaceutical composition comprising the tumor associated antigen of SEQ ID NO:2, for reasons already of record in paper No:15.

Applicant recites *In re Marzocchi* , and argues that there is no statements in the specification that are contrary to generally accepted scientific principles at the time the application was filed. Applicant argues that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In addition, Applicant argues that mere unpredictability of the result of the experiment is not a consideration, and recites *in Re Angstadt*, stating the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the

result of an experiment is not a basis to conclude that the amount of experimentation is undue.

Further, Applicant asserts that the specification cites specific mechanisms for generating peptides and identifying which are immunogenic, using for example prediction algorithms such as the surface probability plot, the hydrophobicity plot, and the antigenic index. Applicant asserts that the specification states that production of antibodies following administration of peptides identified according to the methods known in the art can be measured by common immunological assays, such as ELISA.

The recitation of the case law *In re Marzocchi* and *in Re Angstadt* is acknowledged.

Applicant's arguments set forth in paper No. have been considered but are not deemed to be persuasive for the following reasons:

1. It is noted the 112, first paragraph, enablement rejection has been based on the analysis of the factors set forth in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) and an undue experimentation analysis (See MPEP § § 2164-2164.08(c)) and that unpredictability is one of the factors considered..

The following *Wands* factors have been considered when the 112, first paragraph, enablement rejection was made: 1) The breadth of the claims, 2) The nature of the invention, 3) the state of the prior art, 4) The level of one of ordinary skill, 5) The level of predictability in the art, 6) The amount of direction provided by the inventor, 7) The existence of working examples, and 8) the quantity of experimentation needed to make or use in the invention based on the content of the disclosure.

A) Concerning the breadth of the claims, due to the language "a pharmaceutical composition", the breadth of the claim 33 is overly broad, encompassing a composition for use *in vivo* for treating cancer. B) Concerning the nature of the invention, it would be undue experimentation to practice the claimed invention. Although the polynucleotide of SEQ ID NO:1 encoding the claimed polypeptide of SEQ ID NO:2 is overexpressed in breast and kidney cancer tissues and does not express in the corresponding normal tissues, there is no data nor any correlation showing that SEQ ID NO:1 or the encoded SEQ ID NO:2 is responsible for breast and kidney cancer cell growth, C) Concerning the state of the prior art, treating breast or kidney cancer using SEQ ID NO:2, or fragments thereof, is not known in the art. D) Concerning the level of one of skill in the art, although the level of skill in the field of molecular pathology is high, it would be undue experimentation for one of skill in the art to practice the claimed invention. E) Concerning the level of predictability of the art, cancer therapy is unpredictable, as taught by Gura, Jain, Curti, Hartwell, Ezzell, Spitler, Boon, Sherman et al, all of record, F) Concerning existence of working example, the specification only discloses that the polynucleotide of SEQ ID NO:1 encoding the claimed polypeptide of SEQ ID NO:2 is overexpressed in breast and kidney cancer tissues and does not express in the corresponding normal tissues, and "potential" MHC-binding peptide fragments of SEQ ID NO:2. There is no working example of treating any cancer using SEQ ID NO:2 or fragments thereof, G) Concerning the amount of direction provided by the inventor, the specification does not provide guidance concerning dosage and schedule of treatment. It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed

to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of cancer therapy, as indicated from the teaching of Gura, Jain, Curti, Hartwell, Ezzell, Spitler, Boon, and Sherman et al (all of record), and in view of the complex nature of the invention, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. Concerning an immunogenic fragment of SEQ ID NO:2, wherein said fragment is presented by an MHC-molecule and induces or augments a cellular immune response, or wherein said fragment induces or augments a humoral immune response, there is no disclosure of which fragment actually is presented by an MHC-molecule and induces or augments a cellular immune response specific for SEQ ID NO:2, or which fragment induces or augments a humoral immune response specific for SEQ ID NO:2.

Although the specification discloses peptide fragments of SEQ ID NO:2 that are predicted to bind to MHC molecule, it is unpredictable that said fragments are actually

exposed on the surface of the polypeptide of SEQ ID NO:2, such that members of the immune response such as CTLs and antibodies would recognize the peptide on the surface of the target cancer cells. Roitt et al, 1998, Immunology, 4th ed, Mosby, London, p. 7.7-7.8 teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1). Furthermore, this does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. Further, there is no teaching in the specification of which part of the protein should be used to produce antibodies which will bind specifically to SEQ ID NO:2.

Moreover, as written, claims drawn to short peptide sequences, which are also part of the sequence of SEQ ID NO: 2, encompass claims to defining epitopes of a polypeptide. However, there is no teaching in the specification of whether or not the epitopes are linear or comprise 3-dimensional structures. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes recognized by the claimed invention. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column). The specification has not identified which amino acids and or polypeptide fragments are critical or essential characteristics of the epitope. Moreover, although assay for binding peptides for CTL induction is known in the art, without the knowledge of which amino acids and or polypeptide fragments are critical or essential

characteristics of the epitope, the specification only provides invitation for further experimentation.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

July 18, 2003